

Amendments to the Claims:

1. (Currently amended) An isolated soluble extracellular domain Apo-2 ligand ~~variant~~ polypeptide comprising ~~an amino acids sequence which differs from the native sequence~~ Apo-2 ligand polypeptide sequence ~~39-281~~ of Figure 1 (SEQ ID NO:1) or a fragment thereof and ~~has one or more having one or more~~ of the following amino acid substitutions at the residue position(s) of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; or K179C, wherein said ~~variant~~ polypeptide binds DR4 receptor or DR5 receptor.
  
2. (Currently amended) An isolated soluble extracellular domain Apo-2 ligand ~~variant~~ polypeptide comprising ~~one or more amino acids mutations in the amino acid sequence of native Apo-2 ligand polypeptide sequence 39-281~~ of Figure 1 (SEQ ID NO:1) or a fragment thereof, ~~said mutations comprising one or more and having one or more~~ amino acid substitutions at positions 189, 191, 193, 199, 201, or 209 of the native Apo-2 ligand sequence of Figure 1 (SEQ ID NO:1), wherein said ~~variant~~ polypeptide binds DR4 receptor or DR5 receptor and induces apoptosis in at least one type of mammalian cancer cell.

Claim 3 (Cancelled).

Claim 4 (Cancelled).

5. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 4 wherein said mammalian cell is a cancer cells are lung cancer cells or colon cancer cells.

Claim 6 (Cancelled).

Claim 7 (Cancelled)

8. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 2 wherein said Apo-2 ligand ~~variant~~ polypeptide retains native residues

at positions corresponding to Arg149, Gln205, Val207, Tyr216, Glu236 or Tyr237.

9. (Currently amended) An isolated soluble extracellular domain Apo-2 ligand ~~variant~~ polypeptide comprising ~~an amino acids sequence which differs from the native sequence~~ Apo-2 ligand polypeptide sequence 39-281 of Figure 1 (SEQ ID NO:1) or a fragment thereof and has having a set of amino acid substitutions at the residue position(s) of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) selected from the group consisting of:

Y189A:R191K:Q193K,

Y189A:R191K:Q193K:H264A,

Y189Q:R191K:Q193R:H264R:I266L:D267Q,

Y189A:R191K:Q193K:H264D:I266L:D267Q:D269E, and

Y189A:R191K:Q193R:H264S:I266L:D269E, wherein said polypeptide binds DR4 receptor or DR5 receptor and induces apoptosis in at least one type of mammalian cancer cell.

10. (Currently amended) An isolated soluble extracellular domain Apo-2 ligand ~~variant~~ polypeptide comprising amino acids 39-281 of Figure 1 (SEQ ID NO:1) or a fragment thereof and having one or more amino acid mutations in the amino acid sequence of ~~native~~ Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1), said mutations comprising one or more amino acid substitutions at positions 189, 191, 193, 264, 266, 267, or 269 of the ~~native~~ Apo-2 ligand sequence, wherein said variant polypeptide binds DR4 receptor or DR5 receptor and induces apoptosis in at least one type of mammalian cancer cell.

11. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 10 wherein said Apo-2 ligand ~~variant~~ polypeptide has selective binding affinity for DR5 receptor.

Claim 12 (Cancelled).

Claim 13 (Cancelled).

14. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 11 wherein said DR5 receptor comprises amino acids 1 to 184 of the polypeptide sequence of Fig. 3A (SEQ ID NO:4).

Claim 15 (cancelled)

16. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 10 wherein said Apo-2 ligand ~~variant~~ polypeptide retains native residues at positions corresponding to Arg149, Gln205, Val207, Tyr216, Glu236 or Tyr237.

17. (Currently amended) An isolated soluble extracellular domain Apo-2 ligand ~~variant~~ polypeptide comprising amino acids 39-281 of Figure 1 (SEQ ID NO:1) or a fragment thereof and having one or more amino acid mutations in the amino acid sequence of ~~native~~ Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1), said mutations comprising one or more amino acid substitutions at positions 189, 191, 193, 264, 266, or 267 of the native Apo-2 ligand sequence, wherein said ~~variant~~ polypeptide binds DR4 receptor or DR5 receptor and induces apoptosis in at least one type of mammalian cancer cell.

18. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 17 wherein said Apo-2 ligand variant polypeptide has selective binding affinity for DR5 receptor.

Claim 19 (Cancelled).

Claim 20 (Cancelled)

21. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 18 wherein said DR5 receptor comprises amino acids 1 to 184 of the polypeptide sequence of Fig. 3A (SEQ ID NO:4).

22. (Currently amended) An isolated soluble extracellular domain Apo-2 ligand ~~variant~~ polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence amino acids 39-281 of Figure 1 (SEQ ID NO:1) or a fragment thereof and ~~has~~ having a set of amino acid substitutions at the residue position(s) of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) selected from the group consisting of:

Y189Q:R191K:Q193R; H264R; I266L; D267Q;

Y189Q:R191K:Q193R; and

Y189Q:R191K:Q193R:I266L, wherein said polypeptide binds DR4 receptor or DR5 receptor and induces apoptosis in at least one type of mammalian cancer cell.

23. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of any of claims 1, 2, 4, 5, 7-14, and 8-11, 14, 16-22 18, 21 and 22 wherein said polypeptide is conjugated or linked to one or more polyols.

24. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 23 wherein said polyol is polyethylene glycol.

25. (Currently amended) The Apo-2 ligand ~~variant~~ polypeptide of claim 24 wherein said polyethylene glycol has an average molecular weight of about 1000 daltons to about 25,000 daltons.

26. (Currently amended) An isolated nucleic acid molecule comprising DNA encoding the Apo-2 ligand ~~variant~~ polypeptide of any of claims 1, 2, 4, 5, 7-14, and 8-11, 14, 16-22 18, 21 and 22.

27. (Original) A vector comprising the encoding DNA of claim 26.

28. (Previously presented) An isolated host cell comprising the vector of claim 27, wherein said host cell is an E. coli cell, CHO cell or yeast cell.

Claim 29 (cancelled)

30. (Currently amended) A method of producing Apo-2 ligand ~~variant~~ polypeptide comprising culturing the host cell of claim 28 under conditions sufficient to express said Apo-2 ligand ~~variant~~ polypeptide and recovering said Apo-2 ligand ~~variant~~ polypeptide from said culture.

31. (Currently amended) A composition comprising the Apo-2 ligand ~~variant~~ polypeptide of any of claims 1, 2, 4, 5, ~~7-14, and 8-11, 14,~~ 16-22 18, 21 and 22.

32. (Original) The composition of claim 31 wherein said composition comprises a therapeutically acceptable formulation which contains one or more divalent metal ions.

33. (Currently amended) A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells expressing DR5 receptor or both DR4 and DR5 receptor to an effective amount of Apo-2 ligand ~~variant~~ polypeptide of any of claims 1, 2, 4, 5, ~~7-14, and 8-11,~~ 14, 16-22 18, 21 and 22.

Claims 34-38 (Cancelled).

39. (New) The isolated soluble extracellular domain Apo-2 ligand polypeptide of claim 1 wherein said polypeptide comprises amino acids 114-281 of Figure 1 (SEQ ID NO:1).

40. (New) The isolated soluble extracellular domain Apo-2 ligand polypeptide of claim 2 wherein said polypeptide comprises amino acids 114-281 of Figure 1 (SEQ ID NO:1).

41. (New) The isolated soluble extracellular domain Apo-2 ligand polypeptide of claim 9 wherein said polypeptide comprises amino acids 114-281 of Figure 1 (SEQ ID NO:1).

42. (New) The isolated soluble extracellular domain Apo-2 ligand polypeptide of claim 10 wherein said polypeptide comprises amino acids 114-281 of Figure 1 (SEQ ID NO:1).

43. (New) The isolated soluble extracellular domain Apo-2 ligand polypeptide of claim 17 wherein said polypeptide comprises amino acids 114-281 of Figure 1 (SEQ ID NO:1).

44. (New) The isolated soluble extracellular domain Apo-2 ligand polypeptide of claim 22 wherein said polypeptide comprises amino acids 114-281 of Figure 1 (SEQ ID NO:1).